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None

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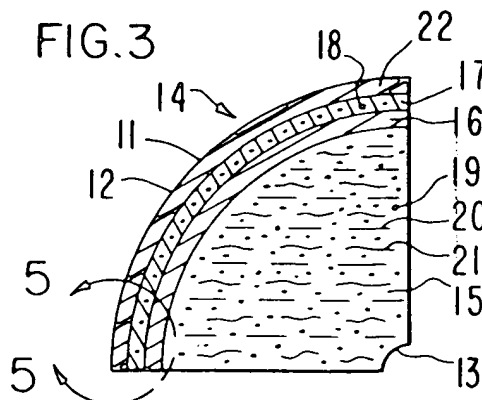
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Selected US specifications from IPC sub-class A61K

(54) Colon delivery system

(57) An osmotic drug device for delivering a drug to the colon comprises a laminated wall (12) surrounding a compartment (15) containing a drug (19) with a passageway (13) through the wall (12) for dispensing the drug from the device. The laminated wall (12) comprises an inner semipermeable lamina (16) and a lamina (17) containing a salt of a fatty acid or a surfactant (18); an optional outer enteric lamina (22) may also be present.



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FIG.1

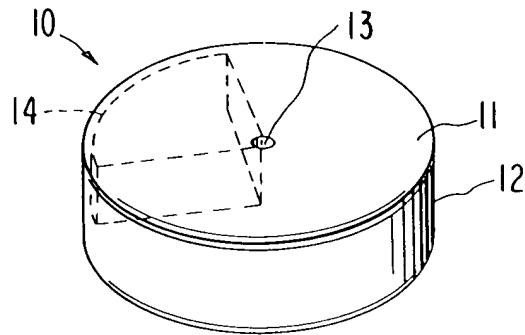


FIG.2

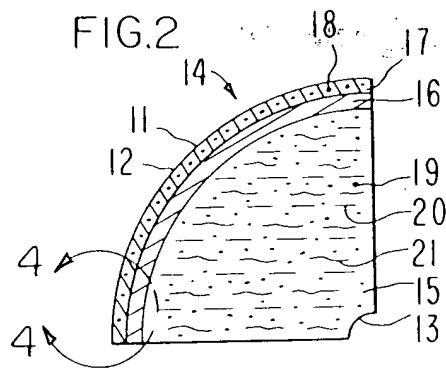


FIG.3

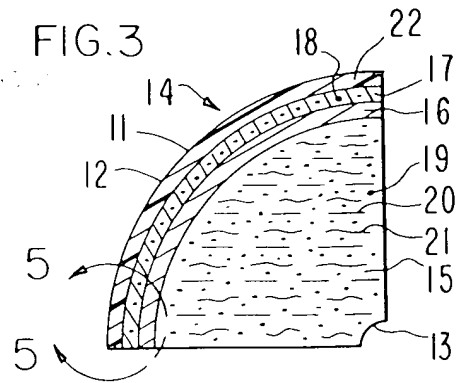


FIG.4

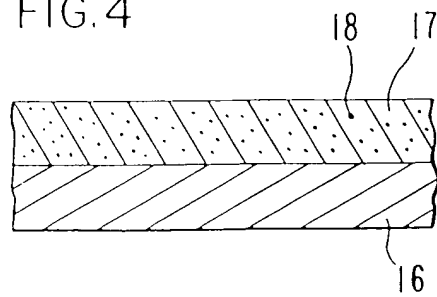
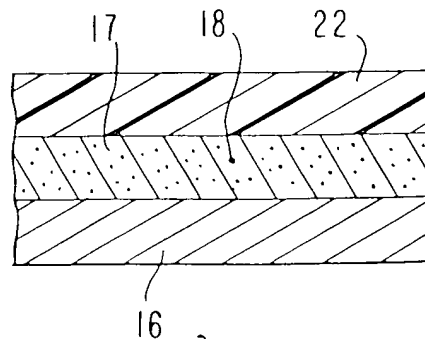


FIG.5



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SPECIFICATION

Colonic therapeutic delivery system

- 5 The present invention pertains to the administration of a beneficially active agent to a preselected region of the gastrointestinal tract, specifically the colon. More particularly, the invention relates to both a novel and useful osmotic delivery system and method for delivering by the oral route a beneficial agent to the colon. The invention concerns also laminates useful for manufacturing the osmotic delivery system. 5
- 10 A continuous need exists for a delivery system for orally administering a beneficial agent in the colon. Such an oral system would be of particular value in the management of ailments, diseases or inflammation of the colon that require colon-targeted administration of a beneficially active agent. That is, the oral delivery system would have a therapeutic value where therapy indicates topical-colon administration of a beneficial agent to an affected colon site. Furthermore 10
- 15 such a system may also provide for systemic absorption of the active agent within the colon. The need for such a delivery system exists where it is therapeutically desirable to delay systemic absorption of the active agent for a predetermined period of time. It will be appreciated that such an oral delivery system which releases an active agent for systemic absorption only in the colon at a preselected time would have a practical value in the management of patients with asthma, 15
- 20 arthritis or inflammation. For example, the delivery system would be administered orally to the patient at bedtime with the system passing through the stomach and the intestine during the night and arriving at the colon, where it commences release in the colon the active agent in the morning, thereby providing the patient with the desired therapy at the appropriate time. 20
- Prior to this invention, tablets, capsules, and the like were orally administered for dispensing an active agent throughout the entire gastrointestinal tract. However, for some drugs a considerable amount of the active agent dispensed by the tablets and the capsules is deactivated by the stomach because of the acidic and enzymatic environment of the stomach. Additionally, most agents are metabolized or absorbed in the small intestine from such immediate release forms. 25
- 30 Consequently, very little of the active agent is available for producing a therapeutic result in the colon. The delivery of active agents through the rectum using suppositories or enemas is often practised in colon therapy; but rectal administration is inconvenient and messy, and is not readily accepted by the patient. Also agent delivery from suppositories cannot reach most of the colon as it is self-limited to the immediate area of administration. 30
- It is immediately self-evident in view of the above presentation, that a need exists for an oral system that delays the onset of delivery for a period of time for the system to reach the colon. Such a period of time corresponds to the time required for the system to transit through the stomach and small intestine and commence delivery of the active agent about the time the system arrives at the colon. 35
- It is an immediate object of this invention to provide a novel osmotic dispensing system for dispensing a useful agent to produce a beneficial effect, which dispensing system overcomes the aforesaid disadvantages associated with the prior art dispensing systems. 40
- It is another object of this invention to provide an osmotic delivery system, for the controlled delivery of a beneficial agent to the colon, and which delivery system represents an advancement in colon-specific therapy.
- 45 It is another object of this invention to provide an oral, osmotic delivery system manufactured in the form of an osmotic device for dispensing a beneficial agent to the colon of the gastrointestinal tract of an animal for both topical and systemic therapy. 45
- It is another object of this invention to provide an osmotic delivery system that delays the onset of agent release from the system for a period of time that approximately corresponds to the time required for the osmotic system to pass through the stomach and the small intestine. 50
- It is another object of this invention to provide a delayed-release osmotic system useful for topical-colonic therapy by the oral route.
- It is another object of this invention to provide a delayed-release osmotic system useful for releasing a drug in the colon for systemic absorption therefrom.
- 55 It is another object of this invention to provide an oral osmotic device comprising a compartment surrounded by a first wall formed of a semipermeable composition, and by a second wall formed of a fluid impermeable composition containing an osmotic solute with the device having an osmotic passageway through both walls. 55
- It is another object of this invention to provide an osmotic device comprising a compartment surrounded by an inner wall formed of a semi-permeable composition, a middle wall formed of a fluid impermeable composition containing an osmotic solute, an outer wall formed of an enteric composition, and a passageway through the walls for delivering a drug from the osmotic device. 60
- It is another object of the invention to provide laminates useful for making osmotic delivery systems.
- 65 According to the present invention, there is provided an osmotic drug delivery device comprising 65

ing

(i) a laminated device wall,

(ii) a compartment defined by said wall and containing a dosage amount of a beneficial drug formulation, and

5 (iii) release means provided in the laminated wall to provide communication between the compartment and the surroundings wherein the device wall comprises

a) a first inner lamina formed from a semipermeable composition, and

10 b) a second lamina comprising a fluid permeable polymer and a salt of a fatty acid or surfactant

the arrangement being such that in its environment of use, fluids in the environment external of the drug device act upon the second lamina of the compartment wall to form a plurality of fluid paths therein to contact the first lamina and to create an osmotic gradient thereacross to cause or allow dispensing of said beneficial drug via said release means.

15 The device in accordance with the invention provides for a delay in the commencement of substantial release of the beneficial drug in view of the time delay resulting from the initial leaching of the second lamina before fluid can commence the establishment of a sufficient osmotic gradient to cause the beneficial drug to be dispensed in any significant amount. The delay can be controlled by controlling the thickness of the second lamina or by the provision of

20 a third lamina which may comprise an enteric composition.

The third lamina may be adapted to erode in the environment of use to allow fluid to contact said second lamina thus delaying the onset of the release of the beneficial drug from said compartment.

In accordance with one embodiment of the present invention, the first semipermeable lamina is

25 formed of a material that does not adversely affect the beneficial agent, and the animal host.

The semipermeable lamina-forming material may be a polymer composition that is permeable to the passage of an external fluid such as water and aqueous biological fluids, while remaining substantially impermeable to beneficial agents and osmotic solutes. The selectively permeable materials forming the semipermeable lamina may be materials that are insoluble in body fluids and they are non-erodible. Typical selective materials for forming said first lamina include semi-

30 permeable polymers, also known to the art as osmosis membranes. The semipermeable polymers include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose ester, cellulose ether and cellulose ester ether. Representative semipermeable polymers include cellulose acetate, cellulose diacetate, cellulose triacetate, dimethylcellulose acetate, cellulose acetate propionate, cellulose acetate butyrate and the like. Semipermeable polymers are known in U.S. Patent Nos.

35 3,173,876; 3,276,586; 3,541,005; 3,541,006; 3,546,142; 3,845,770; 3,916,899; 4,036,228 and 4,111,202 may also be used.

The second lamina may comprise a polymer that is substantially non-toxic, substantially non-erodible, impermeable to the passage of drug formulation, and it is moderately permeable to the

40 passage of fluids present in the environment of use together with a composition capable of being leached from the polymer matrix of the second lamina. In operation, when lamina is in the fluid environment of use, external fluid contacts the outer surface of second lamina and slowly dissolves or slowly leaches the composition therefrom. The process is repeated during the period of time lamina is exposed to external fluid. As the fluid removes composition from said

45 second lamina, the inward progressive removal of composition causes fluid paths to be formed in the lamina. The fluid paths provide a plurality of paths for external fluid to flow through to the semi-permeable lamina. This procedure provides a source of fluid for the operation of first semipermeable lamina.

Exemplary materials for fabricating the second lamina include a member selected from the

50 group consisting of polyolefins, polyvinyls, polyethylenes, polypropylenes, polystyrenes, polyacrylonitriles, polyvinylidene halides and copolymers thereof. Typical materials for fabricating lamina include a member selected from the group consisting of ethylene-vinyl-ester copolymers having an ester content of 4 to 80% such as ethylene-vinyl acetate copolymer, ethylene-vinyl hexanoate copolymer, ethylene-vinyl propionate copolymer, ethylene-vinyl butyrate copolymer,

55 ethylene-vinyl pentanoate copolymer, ethylene-vinyl trimethyl acetate copolymer, ethylene-vinyl diethyl acetate copolymer, ethylene-vinyl-3-methyl butanoate copolymer, ethylene-vinyl-3-dimethyl butanoate copolymer, and ethylene-vinyl benzoate copolymer. Additional exemplary materials suitable for manufacturing lamina include acrylonitrile-methyl vinyl ether, vinyl chloride-diethyl fumarate, plasticized polyvinylchloride, plasticized polyamides, polyisoprene, polyisobutylene,

60 lightly cross-linked polyvinyl pyrrolidone, vinyl-diethyl fumarate copolymer, ethylene-propylene copolymer and the like. The polymeric materials are known in U.S. Patent No. 4,190,642, and in *Handbook of Common Polymers* by Scott et al., 1971 published by CRC Press, Cleveland.

The option third lamina may be made from an enteric material that does not dissolve or disintegrate in the stomach during the period of time the osmotic system passes through the

65 stomach. The enteric materials suitable for forming said enteric lamina include: (a) enteric ma-

terials that are digestible by enzymes in the small intestine; (b) enteric materials containing an ionizable polyacid; (c) enteric materials that are a long-chain polymer with an ionizable carboxyl group, and the like.

- Representative such enteric materials include: (d) a member selected from the group of phthalates consisting essentially of cellulose acetyl phthalate, cellulose diacetyl phthalate, cellulose triacetyl phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether phthalate, methylcellulose phthalate, cellulose ester-ether phthalate and hydroxypropyl cellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, calcium salt of cellulose acetate phthalate, ammonium salt of hydroxypropyl methylcellulose phthalate, cellulose acetate hexahydrophthalate, hydroxypropyl methylcellulose hexahydrophthalate, polyvinyl acetate phthalate, and the like; (e) a member selected from the group consisting of keratin, keratin sandarac-tolu, salol, salol β -naphthyl benzoate and acetotannin, salol with balsam of Peru, salol with tolu, salol with gum mastic, salol and stearic acid and salol and shellac; (f) a member selected from the group consisting of formalized protein, formalized gelatin, and formalized crosslinked gelatin and exchange resins; (g) a member selected from the group consisting of myristic acid-hydrogenated castor oil-cholesterol, stearic acid-mutton tallow, stearic acid-balsam of tolu and stearic acid-castor oil; (h) a member selected from the group consisting of shellac, ammoniated shellac, ammoniated shellac-salol, shellac-wool fat, shellac-cetyl alcohol, shellac-stearic acid-balsam of tolu, and shellac-n-butyl stearate; (i) a member selected from the group consisting of abietic acid, methyl abietate, benzoin, balsam of tolu, sandarac, mastic with tolu and mastic with cetyl alcohol; (j) a member selected from the group consisting of cellulose acetate with shellac, starch acetate phthalate, polyvinyl acid phthalate, 2-ethoxy-5-(2-hydroxyethoxymethyl)-cellulose phthalic acid, acid phthalates of carbohydrates, zein, alkyl resin-unsaturated fatty acids-shellac, colophony mixtures of zein and carboxymethylcellulose; and the like.

The enteric materials are discussed in *Remington's Pharmaceutical Sciences*, 1965 13th Ed., pages 604 to 605, 1965 published by Mack Publishing Co., Eaton, Pa.

- The composition of matter capable of being leached from said second lamina in a preferred embodiment is a salt of a fatty acid. The salt may be selected from the group consisting of an alkali salt, or an alkaline earth salt. The presently preferred fatty acid has from 4 to 26 carbons, including both saturated and unsaturated fatty acids. Representative saturated fatty acids include a member selected from the group consisting of butyric, isovaleric, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, arachidic, behenic, lignoceric and cerotic. Representative unsaturated fatty acids include a member having 10 to 26 carbons and selected from the group consisting of docylenic, dodecylenic, palmitoleic, oleic, ricinoleic, petroselinic, vaccenic, linoleic, linolenic, eleostearic, licanic, parinaric, tariric, gadoleic, archidonic, cetoleic, selacholeic and the like. The alkalies suitable for the present purpose include lithium, sodium, potassium and the like; members of the first group of the periodic system commonly known as alkali metals. The alkaline earths include the elements of second group in the periodic system such as calcium and barium. Exemplary salts of fatty acids include potassium oleate, potassium stearate, sodium stearate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium oleate, sodium palmitate, potassium caprylate, potassium laurate, potassium oleate, calcium ricinoleate, calcium linoleate, calcium linolenate and the like. The composition incorporated in said second lamina includes also anionic, nonionic and cationic surfactants. Representative anionics include carboxylic acids and salts, sulfonic acids and salts, sulfuric acid esters and salts, phosphate esters and salts. Examples of more specific anionic agents include sodium lauryl sulphate, triethanolamine salt of lauryl sulphate, sodium salt of sulfated castor oil, potassium salt of sulfated ricinoleic acid, sodium octyl sulfate, potassium lauryl sulfate, lithium lauryl sulfate, sodium cetyl sulfate and the like. Representative nonionic agents include ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethoxylated fatty acids, and fatty acid amides. Examples of more specific nonionic agents includes sorbitan nonolaurate, sorbitan mono-oleate, mannide mono-oleate, 1:1 capric-diethanolamide, 1:2 lauric acid-diethanolamide condensate and the like. Representative cationic agents include aliphatic mono-, di- and polyamines, amine oxides, substitute amines, alkylammonium salts, salts of heterocyclic amines, arylammonium salts and the like. Examples of more specific cationic agents include lauryldimethylbenzylammonium chloride, laurylisoquinolinium bromide, cetylpyridinium chloride, laurylpyridinium bisulphate, laurylpicolinium p-toluenesulfonate, and the like.

- The compartment containing the beneficial drug formulation may also include an osmotically effective compound; this compound may be an osmotically effective solute, present in said compartment and may comprise one or more members selected from water-soluble inorganic salts and water-soluble organic salts, typically magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, sodium sulfate, potassium acid phosphate and/or choline chloride. The osmotically effective solute can be used for delivering drugs of limited aqueous solubility; the amount of osmotic

solute may be from 0.5% to 25% by weight of the total formulation in said compartment. These osmotically effective compounds are known *per se* see for example U.S. Patent Nos. 4,177,256 and 4,449,983.

Following is a description by way of example only and with reference to the accompanying drawings of methods of carrying the invention into effect.

In the drawings:-

Figure 1 is a view of an osmotic dispensing system designed for orally administering a beneficial agent such as a drug to the colonic region of the gastrointestinal tract. In Fig. 1 a portion of the delivery system is depicted in dashed lines for removing said portion to exhibit the structure of the delivery system.

Figure 2 is a view of the portion depicted in Fig. 1, which portion is removed from the delivery system for illustrating an embodiment of the invention comprising a laminated wall, which system is useful for delivering a beneficial agent to the colon.

Figure 3 is a view of the portion depicted in Fig. 1, removed from the delivery system for illustrating another embodiment of the invention comprising a three layered laminated wall, and which system is useful for delivering a beneficial agent such as a drug to the colon.

Figure 4 illustrates a laminate defining the structural member of the osmotic system taken through 4-4 of Fig. 2.

Figure 5 illustrates a laminate defining the structural member of the osmotic device taken through 5-5 of Fig. 3.

In the drawing figures and in the specification, like parts in related figures are identified by like parts. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

Turning now to the drawings in detail, which drawings are examples of delivery systems provided by the invention and manufactured as osmotic delivery devices, and which examples are not to be construed as limiting, one example of an osmotic device is seen in Fig. 1, identified by the numeral 10. In Fig. 1, osmotic system 10 is sized, shaped and adapted for use as an orally administrable osmotic device, and it comprises a body member 11, a wall 12 and a passageway 13 in wall 11. Fig. 1 depicts also a section 14 that is a portion that can be cut from device 10 for illustrating the structural components of osmotic device 10 only.

In Fig. 2, a section 14 cut from the osmotic device of Fig. 1, is seen for illustrating the structural members of delivery system 10. In Fig. 2 section 14 shows a body 11 and a wall 12 having an osmotic passageway 13, that extends through wall 12, and connects an internal compartment 15 with the exterior of delivery system 10.

Wall 12 of the osmotic system illustrated in Fig. 2, comprises a laminate formed of two laminae, an inner lamina 16 and an outer lamina 17. Inner lamina 16 is directly adjacent compartment 15 and outer lamina 17 is adjacent the exterior of osmotic system 10, on the side thereof remote from compartment 15. Lamina 16, as seen in Fig. 2, comprises a semipermeable composition that is permeable to the passage of an external fluid present in the environment of use, such as aqueous and aqueous like fluids, such as biological fluids. Semipermeable lamina 16 is essentially impermeable to the passage of an active agent such as a drug. Lamina 16 is substantially inert, it maintains its physical and its chemical integrity during the dispensing of a beneficial drug, and it is non-toxic to animals, including humans. Lamina 16 is in laminar arrangement with lamina 17. Lamina 17 is made of a polymeric composition that is non-toxic, and is substantially impermeable to the passage of a beneficial agent such as a drug; it is moderately permeable to the passage of fluids present in the environment of use. Lamina 17 is made from a different polymeric composition than the composition of lamina 16. Lamina 17 additionally comprises a composition of matter 18 that is slightly soluble in the external fluid and it is slowly soluble, or slowly leached from lamina 17, when lamina 17 is contacted by an external fluid. Composition 18 can be homogeneously or heterogeneously dispersed throughout lamina 17. Usually, lamina 17 will contain from about 1 to 70 percent by weight of composition 18, and in a presently preferred embodiment, about 35 to 60 percent by weight.

Compartment 15, in one embodiment, contains a beneficial agent 19, represented in Figs. 2 and 3 by dots, that is soluble or very soluble in an external fluid imbibed into compartment 15. The resulting solution exhibits an osmotic pressure gradient across laminated wall 12 against fluid externally of the wall 12 is imbibed into compartment 15.

In another embodiment, compartment 15 contains a beneficial agent 19 that has limited solubility in fluid 20 imbibed into compartment 15, and in this instance it exhibits a limited osmotic pressure gradient across wall 12, mainly lamina 16 which is semipermeable against the external fluid 20. In this latter embodiment, beneficial agent 19 optionally is mixed with an osmagent 21, indicated by wavy lines, that is soluble in said external fluid to exhibit an osmotic pressure gradient across wall 12 thereagainst.

Fig. 3 depicts another portion of yet another osmotic delivery system 10 provided by the invention. In this embodiment wall 12 of the osmotic system illustrated in Fig. 3 comprises a laminate formed initially of three laminae, an inner lamina 16, a middle lamina 17, and an outer

lamina 22. Inner lamina 16 is adjacent compartment 15 and outer lamina 22 provides the exterior surface of the device. Lamina 16 is formed of a semipermeable composition that is permeable to the passageway of an external fluid and it is essentially impermeable to the passage of active agent 19. Lamina 17 is laminated with lamina 16 and lamina 22. Lamina 17 is formed of a polymeric composition substantially impermeable to the passage of a beneficial agent, and it has distributed therethrough a composition of matter 18 slightly soluble in external fluid. Lamina 22 is formed of an enteric material that does not dissolve or disintegrate in the stomach during the time residence of the osmotic system remains in the stomach, but said enteric lamina 22 disintegrates once the osmotic system 10 enters the small intestine. Compartment 15 of osmotic device 10 comprises a beneficial agent 19, and optionally, an osmotically effective compound 20. During operation, when the osmotic system 10 is in the environment of use dispensing beneficial agent 19, osmotic compartment 15 contains also imbibed external fluid 20. Generally, wall 12 comprises a semipermeable lamina of 25 to 500 microns, an osmotic lamina of 25 to 350 microns, and an enteric lamina of 25 to 200 microns.

Fig. 4 illustrates a view taken through 4-4 of Fig. 2. Fig. 4 depicts wall 12 comprising semipermeable lamina 16 in laminar arrangement with lamina 17 having homogeneously or heterogeneously dispersed throughout lamina 17 slightly aqueous soluble composition 18. Fig. 5 illustrates a view taken through 5-5 of Fig. 3. Fig. 5 depicts wall 12 comprising three-layers in contacting, laminar arrangement. As illustrated, wall 12 comprises semipermeable lamina 16, fluid path forming lamina 17 with composite 18 and enteric lamina 22.

Osmotic delivery system 10 as seen in Fig. 1 through 3 can be made into many embodiments for oral use for releasing locally or systemically acting therapeutic medicaments in the colon of the gastrointestinal tract. The oral system can have various conventional shapes and sizes such as round with a diameter of 1/8 inch to 9/16 inch, or it can be shaped like a capsule having a range of sizes from triple zero to zero and from 1 to 8. In these manufactures, system 10 can be adapted for administering a beneficial agent to warm-blooded mammals, such as humans.

The expression osmotic passageway as used herein comprises means and methods suitable for releasing a beneficial agent 19 from compartment 15. The osmotic passageway or orifice will pass through the laminated wall for communicating with compartment 15. The expression for passageway includes passageways formed by mechanical drilling or laser drilling through the laminated wall. Generally, for the purpose of the invention, the passageway will have a maximum cross-sectional area, A, defined by the equation

$$\frac{L}{F} \times \frac{Q_v}{t} \times \frac{1}{DS} \quad (1)$$

wherein L is the length of the passageway (Q_v/t) is the mass delivery rate of agent D released per unit time, D is the diffusion coefficient of the agent in the release solution, S is the solubility of the agent in the fluid and F has a value of approximately 2 to 1000, said osmotic passageway having a minimum area, A_{\min} , defined by the equation

$$\left[\frac{Lv}{t} \times 8 \times \frac{\pi \eta}{\Delta P} \right]^{1/2} \quad (2)$$

wherein L is the length of the passageway, v/t is the volume of the agent released per unit of time, π is 3.14, η is the viscosity of the solution being released, and ΔP is the hydrostatic pressure difference between the inside and the outside of the compartment and having a value up to 20 atmospheres. The dimensions for the osmotic passageway is disclosed in U.S. Patent No. 3,916,899.

The term beneficial agent as used in this specification and the accompanying claims includes drugs that are pharmacologically active, that produce, when released in the colon, a local or a systemic beneficial, therapeutic effect. The active drug that can be delivered includes inorganic and organic beneficially active compounds, such as materials that act on the nervous system, hypnotics, sedatives, physic energizers, tranquilizers, anticonvulsants, muscle relaxants, anti-ulcer, anti-asthmatics, CNS stimulants, antiparkinson agents, analgesics, anti-inflammatory, anesthetics, antimicrobials, antipyretics, and the like. The beneficial drugs are known to the medical art in *Pharmaceutical Sciences*, by Remington, 14th Ed., 1970, published by Mack Publishing Co., Easton, Pa., in *American Drug Index*, 1976 published by J. B. Lippincott Co., Philadelphia, Pa., in *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, 1974-1976 by Falconer et al., published by Saunder Company Philadelphia, Pa., and in *Medical Chemistry* 3rd Ed., Vols. 1 and 2 by Burger, published by Wiley Interscience, New York.

The osmotic devices of the invention may be manufactured by mixing the drug with drug formulation ingredients by ballmilling, calendering, stirring and pressing into a preselected shape

having a shape that corresponds to the shape of the final osmotic device. The semipermeable material forming the first lamina can be applied by dipping, molding, or spraying the pressed mixture. One procedure for applying a wall-forming material is the air suspension procedure. The air suspension technique can be used for manufacturing a wall formed of a single layer, or
 5 formed of a multiplicity of layers. The air procedure is described in U.S. Patent No. 2,799,241; in *J. Am. Pharm. Assoc.*, Vol. 48, pages 451 to 459, 1959 and in *ibid*, Vol. 49, pages 82 to 84, 1960. Procedures for measuring the surface area diameter of solutes are reported in *Journal Amer. Cham. Soc.*, Vol. 60, 309 to 319, 1938; *The Surface Chemistry of Solids*, by Gregg, 2nd Ed., 1961, published by Reinhold Corp., New York; *Absorption, Surface Area and Porosity*, by
 10 Gregg et al., 1967, published by Academic Press, New York; *Physical Absorption of Gases*, by Yound et al., 1962, published by Butterworth & Co., London; and *Fine Particle Measurements*, by Valla, 1959, published by Macmillan, New York. The osmotic pressure of solutes can be measured in a commercially available osmometer that measures the vapor pressure differences between pure water and the solution containing a solute to be analyzed and according to
 15 standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. An osmometer that can be used for osmotic pressure measurements is identified as Model 302B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avondale, Pa. Procedures for measuring aperture formation in lamina 16 by osmotic solute generating
 20 hydrostatic pressure in depot 17 exceeding the cohesive integrity of the polymer with the formation of fluid channels can be determined by measurements predicated on pressure deflection and mechanical behaviour measurement techniques are reported in *Modern Plastics*, Vol. 41, 143 to 144, 146 and 182, 1964; *Handbook of Common Polymers*, by Scott et al., 588 to 609, 1971, published by CRC Press, Cleveland, Ohio; *Machine Design*, 107 to 111, 1975; *J. Sci. Instruments*, Vol. 42, 591 to 596, 1965; and by measuring mechanical stress-strain patterns of
 25 polymers using the Instron Testing Machine, available from Instron Corp., Canton, Mass., and by using the procedures disclosed in U.S. Patent Nos. 4,177,256; 4,190,642; 4,298,003 and 4,265,874.

Exemplary solvents suitable for manufacturing the walls include inert inorganic and organic solvents that do not adversely harm the wall forming materials, the drug, the agent, and the final
 30 device. The solvents broadly include aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetate, ethyl acetate, methyl isobutyl ketone, n-hexane, ethylene glycol monoethyl acetate, carbon tetrachloride, methylene chloride, ethylene dichloride, propylene dichloride, cyclohexane, mixtures such as acetone and water, acetone and methanol,
 35 acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and mixtures thereof.

EXAMPLE

A drug composition of 5-amino-salicylic acid is prepared for housing in the compartment of an
 40 osmotic device by thoroughly blending 200 mg of 5-amino salicylic acid, 20 mg of lactose, 10 mg of polyvinyl pyrrolidone, 20 mg of sodium chloride and 3 mg of magnesium stearate and then compressing the homogeneous blend into a precompartment-forming drug formulation.

The compressed drug formulation is placed in an air suspension machine and coated with a semipermeable lamina-forming composition. The semipermeable lamina-forming composition comprises 80% by weight of cellulose acetate having an acetyl content of 39.8% and 20% by
 45 weight of cellulose acetate having an acetyl content of 32%. The semipermeable lamina is applied from a solvent mixture comprising methylene chloride and 95% ethanol, 80:20 wt:wt. The semipermeable lamina coated drug is then air dried in a forced air oven at 50°C overnight.

A slurry of ethylene-vinyl acetate copolymer having a vinyl acetate content of 40% is prepared
 50 by mixing the copolymer in methylene chloride and adding thereto 35 g of sodium lauryl sulfate. The coated drug is submerged into the copolymer slurry. Upon removal from the slurry a layer of the copolymer containing the anionic sodium lauryl sulphate remains as a coating on the exterior surface of the semipermeable cellulose acetate. The laminated coated compartment is dried in a forced air oven at 50°C for about 18 hours.

After drying, an enteric lamina is applied by placing the two-layered laminated-coated drug into
 55 a pan containing shellac. The shellac should be U.S.P. grade, and should be sufficient to wet thoroughly the entire surface of the ethylene-vinyl acetate copolymer lamina. After the entire surface has been coated with the shellac, the drug device so formed is removed from the pan and dried at 50°C. A second coating of shellac is applied in the same way as the first. On
 60 completion of the application of the second coating, the three-layered drug device is then dried in a forced air oven at 50°C for one week.

An osmotic passageway is laser drilled through the three laminae connecting the compartment with the exterior of the device. The osmotic passageway has a diameter of 9 mils for delivering the drug from the device.

65 An oral osmotic device for the delivery of 5-amino-salicylic acid to the colon is prepared by

following the above procedure with all conditions as previously described, except that sodium lauryl sulfate is replaced with 45 g sodium stearate.

CLAIMS

- 5 1. An osmotic drug delivery device comprising 5
 - (i) a laminated device wall,
 - (ii) a compartment defined by said wall and containing a dosage amount of a beneficial drug formulation, and
 - (iii) release means provided in the laminated wall to provide communication between the
- 10 compartment and the surroundings 10
 - wherein the device wall comprises
 - a) a first inner lamina formed from a semipermeable composition, and
 - b) a second lamina comprising a fluid permeable polymer and a salt of a fatty acid or surfactant
- 15 the arrangement being such that in its environment of use, fluids in the environment external of 15
 the drug device act upon the second lamina of the compartment wall to form a plurality of fluid paths therein to contact the first lamina and to create an osmotic gradient thereacross to cause or allow dispensing of said beneficial drug via said release means.
2. A device as claimed in claim 1, wherein the compartment wall includes a third lamina, said 20
 third lamina comprising an enteric composition in laminar arrangement with said second lamina. 20
3. A device as claimed in claim 2 wherein the third lamina is adapted to erode in the 25
 environment of use to allow fluid to contact said second lamina thus delaying the onset of the release of the beneficial drug from said compartment.
4. A device as claimed in any preceding claim wherein the first lamina is formed of a 25
 member selected from cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose ester, cellulose ether, cellulose ester-ether, cellulose acetate, cellulose diacetate and cellulose triacetate.
5. A device as claimed in any preceding claim wherein the second lamina is selected from 30
 one or more of a polyolefin, polyvinyl, polystyrene, polyacrylonitrile and polyvinylidene halide.
6. A device as claimed in any one of claims 2 to 5 wherein the third lamina is formed of a 30
 member selected from the group consisting of cellulose acetyl phthalate, cellulose diacetyl phthalate, cellulose triacetyl phthalate, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, cellulose ester phthalate, cellulose ether phthalate, sodium cellulose acetate phthalate, methyl cellulose phthalate and hydroxypropyl cellulose phthalate.
7. A device as claimed in any preceding claim wherein the surfactant or fatty acid salt of the 35
 second lamina is one or more compounds selected from alkali salts and alkali earth salts of saturated and unsaturated fatty acids having 4 to 26 carbon atoms and anionic, cationic and non 35
 ionic surfactants.
8. A device as claimed in claim 1 and substantially as herein described with reference to and 40
 as illustrated in the accompanying drawings.
9. Each and every novel embodiment herein set forth. 40

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